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Granulocyte-Macrophage Colony-Stimulating Factor in Association With High-Dose Chemotherapy (VETOPEC) for Childhood Solid Tumors: A Report From the Australia and New Zealand Children's Cancer Study Group

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Purpose. Combination chemotherapy with vincristine, etoposide, and high-dose, escalating cyclophosphamide (VETOPEC) is an effective regimen in pediatric patients with high-risk solid tumors. The toxicity of the regimen is predominantly haematologic. This study addressed the role of recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) following each cycle of chemotherapy in decreasing neutropaenia, incidence of fever/hospitalization, and/or increasing chemotherapy dose-intensity.

Patients and Methods. Twenty-nine children with recurrent solid tumors were treated with the VETOPEC regimen. Sequential cohorts of patients received no GM-CSF (Group I), or GM-CSF in a dosage of 5 μg/kg/day (Group II) or 10 μg/kg/day (Group III) on days 4–18 of each chemotherapy cycle. Up to four cycles of chemotherapy were analysed with respect to haematopoietic recovery, clinical parameters, and dose intensity.

Results. Neutrophil recovery was significantly more rapid in patients treated with GM-CSF. Time to achieving an absolute neutrophil count (ANC) over 0.5×10^9/L in Groups I, II, and III were 21, 18, and 16 days, respectively ($P < 0.0001$). Time to achieving an absolute neutrophil count (ANC) over 1.0×10^9/L in Groups I, II, and III were 24, 19, and 17 days, respectively ($P < 0.0001$). There was no significant difference in the incidence of febrile neutropaenia between the three groups. Febrile neutropaenia occurred following 42, 68, and 62% of chemotherapy cycles in Groups I, II, and III, respectively ($P = 0.27$). Chemotherapy dose intensity was not different between the three groups. GM-CSF was associated with pericarditis and myalgias in one patient, and transient hypoxia/hypotension in another.

Conclusion. GM-CSF led to significantly more rapid neutrophil recovery following VETOPEC chemotherapy, but did not lead to any demonstrable clinical benefit, either in reducing febrile events, or in increasing chemotherapy dose intensity. Med. Pediatr. Oncol. 29:108–114, 1997. © 1997 Wiley-Liss, Inc.

INTRODUCTION

The haematopoietic growth factors are a group of cytokines that play a key role in the regulation of blood cell proliferation and differentiation. They include the interleukins, erythropoietin, the colony stimulating factors (CSFs), and a variety of other molecules. Recombinant CSFs, particularly granulocyte-macrophage colony-stimulating factor (GM-CSF) [1–3] and granulocyte colony-stimulating factor (G-CSF) [4,5], have been developed for clinical use and have been studied in several clinical settings in an effort to enhance neutrophil numbers and function. Areas of study have included disease states such as congenital or acquired neutropaenias [6], and treatment-related neutropaenia following high-dose chemotherapy or bone marrow transplantation [3,5,7–9].

The Australia and New Zealand Children's Cancer Study Group recently reported a high response rate in a heterogeneous group of relapsed or progressive childhood solid tumors using the VETOPEC regimen, which combined vincristine, etoposide, and high-dose fractionated and escalating cyclophosphamide [10]. The relatively low non-haematologic toxicity of cyclophosphamide and etoposide makes them suitable agents for dose

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intensification strategies, which may be better tolerated with the use of cytokine support. The original VETOPEC regimen was designed without use of cytokine, but the protocol was amended in July 1992 to incorporate the use of GM-CSF. At that time the haematologic toxicity and relevant sequelae of the regimen had been well established, allowing comparisons with specific reference to amelioration of neutropaenia and infection and/or improvement in dose intensity (DI). We now report our experience with the use of GM-CSF in the context of VETOPEC therapy and compare the sequential cohorts of patients treated with or without cytokine.

PATIENTS AND METHODS

Criteria for Eligibility and Patient Population

Patients eligible for this study were aged less than 20 years, had histologically confirmed recurrent or refractory solid tumor following previous chemotherapy, and were considered able to tolerate at least two courses of intensive chemotherapy. Of the population treated on the VETOPEC protocol, 29 patients were enrolled in this analysis between May 1991 and May 1994. In July 1992 a protocol amendment led to the use of recombinant GM-CSF (Schering-Plough, Sydney, Australia) following each course of therapy. Accordingly, 10 patients were treated with chemotherapy only (Group I) and 19 patients received chemotherapy and GM-CSF as described below (Groups II and III). Protocols were approved by the institutional ethics committees and informed consents were obtained from patients and/or parents as appropriate.

Therapy

The chemotherapy cycles consisted of vincristine 0.05 mg/kg (maximum 1.9 mg) by intravenous push on days 1 and 14, and etoposide 2.5 mg/kg/day infused over 2 hours on days 1, 2, and 3, followed by cyclophosphamide infused over 6 hours on days 1, 2, and 3, in conjunction with mesna and double maintenance fluids. A maximum of six cycles were delivered. Because the numbers of patients receiving five or six cycles were small, this report includes analysis of cycles 1–4 only. The cyclophosphamide dosage in cycle 1 was 30 mg/kg/day for each of the 3 days; in subsequent cycles of each patient, the dose was increased by 5 mg/kg/day up to a maximum of 55 mg/kg/day. Cycles were scheduled to repeat every 21–28 days if marrow recovery had occurred (absolute neutrophil count [ANC] $>1.0 \times 10^9$/L, platelet count $>100 \times 10^9$/L). If an interval of more than 35 days before starting the next cycle was experienced with two successive cycles, the cyclophosphamide dosage was decreased to that which had previously not led to delays, and escalation was ceased. Prophylactic co-trimoxazole was administered daily.

Patients in Groups II and III received GM-CSF by daily subcutaneous injection on days 4–18 of each cycle. An interval of 24 hours was required between the completion of chemotherapy and the first dose of GM-CSF in each cycle. Groups II and III were sequential cohorts of patients receiving GM-CSF 5 and 10μg/kg/day on days 4–18, respectively.

At completion of the protocol, or earlier if rapid response was documented, patients proceeded to the next phase of treatment according to investigator choice. Approaches included combinations of surgical resection of residual tumor, radiation therapy, and further chemotherapy with or without autologous bone marrow transplantation (ABMT).

Evaluation of Tumor Response and Toxicity

Disease status was re-evaluated after every 2–3 cycles using the appropriate combination of physical examination, radiologic and/or radio-nuclide imaging, histopathology, cytology, and tumor marker analyses. Tumor responses were defined by standard criteria: complete response (CR) was defined as disappearance of all clinical, radiologic, and biochemical evidence of tumor. Partial response (PR) was a greater than 50% reduction in the sum of the products of the largest perpendicular diameters of all lesions with no evidence of new lesions. Stable disease (SD) was a less than 50% reduction and less than 25% increase in size, and progressive disease (PD) a greater than 25% increase in these dimensions or the appearance of new lesions. Reduction in tumor size had to be maintained for at least 1 month for allocation of response status. Response durations were calculated from time of documentation of first response. Patients with PD after two or more cycles were taken off study.

Haematologic toxicity was monitored with full blood counts performed routinely 1–2 times weekly and more frequently during periods of fever. The frequency of routine full blood counts was increased from once to twice per week following the introduction of GM-CSF. Urinalysis, biochemical profile, and chest X-ray were performed before each cycle. Echocardiography with measurement of ejection fraction was performed before every second cycle. Patients developing fever over 38.5°C in association with neutropaenia ($ANC < 0.5 \times 10^9$/L) were hospitalised and treated with broad spectrum intravenous antibiotics.

Statistical Methods

The Kruskal-Wallis test statistic was used to test for differences between the three groups in blood count and clinical parameters. Additionally, the Mann-Whitney U-test was used where indicated for comparisons between two groups. Clinical parameters analysed were: age, number of cycles of chemotherapy evaluated, days between successive cycles of chemotherapy, cumulative DI of cyclophosphamide, and proportion of cycles for each

patient, which were followed by admission to hospital with fever and neutropaenia. Specific haematologic parameters analysed were times in each cycle to ANC exceeding and remaining above 0.2, 0.5, and 1.0 × 10^9/L, and platelet count exceeding 100 × 10^9/L, not attributable to platelet transfusion. In cases where cytopaenias did not fall below the defined cut-off values, the time from day one of the cycle to the end of the nadir was used to indicate recovery. The rapid rise in ANC, which occurs after cytokine treatment, makes it possible to miss the exact day on which recovery to a given level occurs. In the absence of daily full blood counts, we considered cycles non-evaluable for recovery to any given level if, at the time of testing, the ANC had risen to more than double the target cut-off value. This method is expected to exclude from the analysis estimates of the interval that exceed the real value by more than 1–2 days. The proportion of non-evaluable cycles in patients treated without and with GM-CSF were compared using the chi-squared test. Cyclophosphamide DI was expressed as % scheduled DI, and was calculated for each patient by dividing total CPA administered by duration of therapy on study, and comparing this to the CPA DI which would be achieved if protocol CPA escalation occurred, with cycles at 21-day intervals. Accrual was intended to achieve numbers in each of the GM-CSF cohorts comparable to the existing control group, and grant funding was received accordingly.

RESULTS

Patient Characteristics

Twenty-nine patients from nine centres, treated with the VETOPEC protocol, were evaluated. These included ten patients who received no GM-CSF (or other cytokine) (Group I), eight who received GM-CSF in a dosage of 5 μg/kg/day (Group II) and eleven who received GM-CSF 10 μg/kg/day (Group III). Patient characteristics including age, diagnosis, and prior therapy are summarised in Table I. The three groups were comparable with respect to these parameters. The median age was lower in patients receiving GM-CSF but this difference was not significant either across the three groups ($p = 0.57$), or when Group I was compared with Groups II and III combined ($p = 0.37$).

TABLE I. Characteristics at Commencement of Study and Prior Therapy of 29 Patients With Solid Tumors Enrolled in VETOPEC Study

	Group I	Group II	Group III
GM-CSF daily dose	None	5 μg/kg	10 μg/kg
n	10	8	11
Age (median*)	11.5	5.5	6.3
(Range)	1.8–19	2–17	0.8–15
Diagnoses			
Wilms' tumor	2	2	3
Rhabdomyosarcoma	2	1	4
Non-Hodgkin's	2	0	0
Neuroblastoma	2	0	1
Hodgkin's disease	1	0	0
Brain tumors	0	2	2
Ewings sarcoma/PNET	1	2	0
Osteosarcoma	0	1	1
Prior regimens			
1	8	6	10
2	1	2	1
>2	1	0	0

*$p = 0.57$ by Kruskal-Wallis test statistic.

Chemotherapy Administered

Although some patients received up to six cycles of therapy, this report includes data on cycles 1–4 only. A total of 90 cycles of the study protocol are included in this analysis with a median of three cycles being analysed per patient. Total cycles administered to Groups I, II, and III were 34, 26, and 30, respectively. The median number of cycles analysed in the three groups was: three in Group I, four in Group II, and two in Group III ($P = 0.21$). One patient in Group II received only one cycle; the remaining patients received two or more cycles. Overall, protocol doses of cyclophosphamide were administered in 92% of cycles and the median interval between cycles was 27 days. There was no significant difference between the groups with respect to success of dose escalation of cyclophosphamide, number of days between cycles and cyclophosphamide DI (Table II).

Haematologic Efficacy

Sequential blood counts were recorded between treatment cycles for all patients. Overall, 36% of cycles were non-evaluable for neutrophil recovery to the various cut-off values. These comprised 43 and 32% of cycles given without and with GM-CSF, respectively, a difference which was not statistically significant ($P > 0.05$). Patients receiving GM-CSF experienced more rapid neutrophil recovery (Table III). The median time to ANC exceeding 0.2 × 10^9/L for Groups I, II, and III combining cycles 1–4 was 18, 16, and 15 days, respectively ($P = 0.0001$). Times to ANC exceeding 0.5 × 10^9/L for these groups were 21, 18, and 16 days, respectively ($P < 0.0001$), and times to ANC exceeding 1.0 × 10^9/L were 24, 19, and 17 days, respectively ($P < 0.0001$). The difference in time to neutrophil recovery between Groups II and III was also significant when analysed using the Mann-Whitney U-test ($P = 0.01$, 0.002, and 0.006 for 0.2, 0.5, and 1.0 × 10^9/L, respectively).

Time to platelet recovery, as assessed by number of days to a platelet count exceeding 100 × 10^9/L was significantly different between the three groups. The median time to platelet recovery was 21.5, 23.5, and 18 days in Groups I, II, and III, respectively ($P = 0.02$). Using the

TABLE II. Chemotherapy Delivered and Dose-Intensity Achieved in the Three Groups: Group I Receiving No GM-CSF (*n* = 10), Group II Receiving 5 μg/kg/day GM-CSF (*n* = 8), and Group III Receiving 10μ g/kg/day GM-CSF (Group III; *n* = 11)

	Group I	Group II	Group III	*P* value*
Total cycles administered	34	26	30	
Cycles per patient (median)	3	4	2	0.21
(range)	(2–4)	(1–4)	(2–4)	
Median interval in days between cycles (median)	28	28	24	0.12
(range)	(14–42)	(21–44)	(21–38)	
% scheduled cumulative DI[a]				
Cycles 1–2 (median)[b]	82%	86%	84%	0.6
(range)	(60–105%)	(69–91%)	(75–100%)	
Cycles 1–3/4 (median)[c]	68%	72%	79%	0.5
(range)	(63–103%)	(64–76%)	(73–87%)	

[a]Scheduled DI was based on protocol escalation of cyclophosphamide and 21-day intervals between cycles.
[b]Dose-intensity achieved over the duration of the first 2 cycles of therapy, i.e., from study entry to first day of cycle 3.
[c]Dose-intensity achieved over the duration of the first 3–4 cycles of therapy, i.e., from study entry to first day of cycle 4 or 5, depending on number of cycles administered to patient.
**P* values calculated for the comparison of the three groups using the Kruskal-Wallis test statistic. Differences in cycle interval and DI between Groups I and II/III (combined), or between Groups I/II (combined) and III were not significant when analyzed using the Mann-Whitney U-test.

TABLE III. Times to Neutrophil and Platelet Recovery, and Incidence of Febrile Neutropaenia in Cycles 1–4 for the Three Groups: Group I Receiving No GM-CSF (*n* = 10), Group II Receiving 5 μg/kg/day GM-CSF (*n* = 8), and Group III Receiving 10 μg/kg/day GM-CSF (*n* = 11)

	Group I	Group II	Group III	*P* value
Neutrophil recovery[a]				
Days to ANC > 0.2×10^9/L	18 (16–27)	16 (13–23)	15 (10–18)	0.0001
Days to ANC > 0.5×10^9/L	21 (17–32)	18 (15–26)	16 (11–23)	<0.0001
Days to ANC > 1.0×10^9/L	24 (17–43)	19 (15–35)	17 (11–28)	<0.0001
Platelet recovery[a]				
Days to plats > 100×10^9/L	21.5 (10–41)	23.5 (11–38)	18 (9–29)	0.02
Proportion of courses associated with fever	42%	68%	62%	0.27

[a]Values represent the median and (range).

Mann-Whitney U-test, the only significant difference between any two groups in terms of platelet recovery was between Groups II and III ($P = 0.004$).

Because of the possibility that the higher number of cycles of chemotherapy administered to the patients in Groups I and II may have led to slower recovery times in later cycles due to cumulative high-dose chemotherapy exposure and therefore biased the analysis in favor of Group III, we also performed analyses of haematologic recovery in cycles 1–2 only (Table IV). The time to neutrophil recovery (i.e., days till ANC > 0.2, 0.5, or 1.0 $\times 10^9$/L) remained significantly shorter in patients treated with GM-CSF (Table III). However, while there was a trend towards more rapid neutrophil recovery at the 10 μg/kg/day dose of GM-CSF than at the 5 μg/kg/day dose, this difference was significant only for ANC > 1.0 $\times 10^9$/L when these two groups were compared using the Mann-Whitney U-test ($P = 0.05$). The pattern of platelet recovery between the three groups in cycles 1–2 was similar to that described for cycles 1–4.

Infections

There were no significant differences between the three groups in the frequency of admission to hospital with fever and neutropaenia. Overall, 56% of cycles led to admission with fever. Rates of fever/neutropaenia for Groups I, II, and III were 42, 68, and 62%, respectively ($P = 0.27$). A comparison of Group I with Groups II and III combined (i.e., no GM-CSF vs. 5 or 10 μg/kg/day GM-CSF) revealed no significant difference in the frequency of fever and neutropaenia ($P = 0.11$). Two patients died while on the study. One patient each from Groups I and II died of sepsis, both following three cycles of therapy.

TABLE IV. Times to Neutrophil and Platelet Recovery in Cycles 1–2 for the Three Groups: Group I Receiving No GM-CSF (n = 10), Group II Receiving 5 μg/kg/day GM-CSF (n = 8), and Group III Receiving 10 μg/kg/day GM-CSF (n = 11)

	Group I	Group II	Group III	P value
Neutrophil recovery				
Days to ANC > 0.2×10^9/L	18 (16–22)	15 (13–21)	15 (10–22)	0.003
Days to ANC > 0.5×10^9/L	20 (17–28)	17.5 (15–24)	16 (11–26)	0.002
Days to ANC > 1.0×10^9/L	23 (17–31)	18 (15–27)	16.5 (11–26)	0.0004
Platelet recovery				
Days to plats > 100×10^9/L	17 (10–27)	22.5 (11–29)	18 (9–21)	0.02

*Values represent the median and (range).

Non-Haematologic Toxicity

One patient receiving GM-CSF at the 5 μg/kg/day dose developed acute pericarditis with a small pericardial effusion documented by echocardiography. His symptoms and echocardiographic findings resolved following cessation of GM-CSF. This patient also experienced myalgias requiring treatment with paracetamol. One patient in Group III developed transient hypotension and hypoxia following the first dose of GM-CSF.

Tumor Response

Of the 29 patients included in this study, 24 are evaluable for tumor response. Fourteen patients responded to the study regimen. The overall response rate (PR + CR) was 58%. In Groups I, II, and III, responses were seen in 8/10, 2/5, and 4/10 evaluable patients, respectively. A more detailed analysis of phase II end-points is the subject of a separate report.

DISCUSSION

The combination of vincristine, etoposide, and cyclophosphamide as used in this study has been shown to be a highly effective regimen. We initially reported tumor responses in 19 of 20 evaluable patients with advanced or recurrent solid tumors in childhood following treatment with the VETOPEC regimen.[10] In that report, the principal toxicity was myelosuppression, with 54% of cycles of therapy being complicated by subsequent admission to hospital with fever and neutropaenia. The purpose of this study was to investigate whether the use of GM-CSF led to any amelioration of neutropaenia and infective complications, or could lead to greater chemotherapy DI. We found that GM-CSF administration at either of two dose levels led to significantly more rapid neutrophil recovery, but that this improvement in neutrophil numbers was not accompanied by any demonstrable clinical benefit.

We compared three sequential cohorts of patients receiving the VETOPEC protocol, with no GM-CSF, with 5 μg/kg/day GM-CSF, or with 10 μg/kg/day GM-CSF, following each course of chemotherapy. Neutrophil recovery to an ANC of 0.2, 0.5, or 1.0×10^9/L was significantly more rapid in patients receiving GM-CSF, with the higher dose of GM-CSF being most effective in enhancing neutrophil recovery. Achievement of an ANC greater than 1.0×10^9/L occurred 6–7 days earlier in patients receiving this higher dose of GM-CSF than in patients receiving no cytokine, and 1–2 days earlier than those patients receiving the lower dose of GM-CSF. A dose-response relationship between GM-CSF and neutrophil recovery has been described previously [2].

Despite significantly improved neutrophil recovery, patients receiving 5 μg/kg/day or 10 μg/kg/day GM-CSF were admitted to hospital with fever following 68 and 62% of cycles, respectively, compared to 42% of cycles in the control group. This difference was not statistically significant, but is disappointing in view of the enhancement of haematologic parameters noted above. Similar findings were reported by investigators at St. Jude Children's Hospital in a study of GM-CSF use following chemotherapy with ifosfamide, carboplatin, and etoposide (ICE) [3]. They found that 79% of cycles of ''ICE-only'' were followed by admission to hospital with fever, compared to 100% of cycles with GM-CSF, a difference that was not significant. They speculated that the known association of GM-CSF with fever as a side effect might explain the failure of GM-CSF to reduce hospital stays despite significant improvements in neutrophil numbers. GM-CSF-related fever was more common at higher dosages in the dose-ranging study of Hamm et al. [8]. On the other hand, an earlier report from the St. Jude group, and studies from other centres have described reductions in the need for inpatient care following the addition of GM-CSF [2,8,9,11]. It may be that larger numbers of patients need to be treated to detect a statistically significant clinical benefit.

Additionally, no enhancement of chemotherapy DI was achieved following the addition of GM-CSF. The accuracy of this finding may be limited by the minimum 21-day cycle interval mandated in the protocol, and practical issues such as hospital bed availability. Improvements in DI may have been demonstrable, for instance, if the next cycle commenced whenever haematologic parameters were reached. However, other factors affect

timing of chemotherapy cycles and the capability of cytokine to lead to enhancement of DI. The patient's clinical status and the need to eradicate infections before embarking on further myelosuppressive therapy may be valid obstacles. Nonetheless, use of GM-CSF or G-CSF has led to improvements in DI in some studies [12–14].

We found that the higher dose of GM-CSF was associated with significantly more rapid platelet recovery than the lower dose. However, the use of *no* GM-CSF was intermediate in this regard, albeit not significantly different to the 5 μg/kg/day dose level. Findings in other clinical studies regarding platelet recovery following GM-CSF use have been variable [8,15–17], but a dose-response relationship between GM-CSF and platelet recovery was noted in one pediatric trial [2]. Furthermore, there is in vitro evidence of such a relationship between GM-CSF and megakaryocytes, with effective concentrations proposed to be much higher than those required for the stimulation of granulocyte/macrophage colonies [17]. On the other hand, a study of adult patients with lung malignancies receiving chemotherapy and radiation therapy revealed significant *increases* in the incidence of severe thrombocytopaenia in patients randomised to receive GM-CSF [18]. The presence of sepsis may also delay platelet recovery, a potential contribution we were not able to address adequately in our series.

Tumour response was not a primary end-point of this analysis. Nonetheless, it is interesting to note that the tumour response rate was lower in the patients receiving GM-CSF. While the numbers of patients preclude any conclusions in our study, others have reported lower, though not significantly lower, response rates in patients receiving GM-CSF for small-cell lung cancer [18]. Patients in that study receiving GM-CSF had had greater chemotherapy dose reductions than control patients, and overall survival was similar, but the authors could not exclude a detrimental effect of GM-CSF on tumour response in a minority of patients. In this regard, the previously reported presence of receptors for GM-CSF and other haematopoietic cytokines in a small minority of non-haematopoietic cancer cells, and stimulation of growth of some cell lines in vitro by growth factor, was noted by the authors [18–23].

In summary, we have found significantly enhanced neutrophil recovery following VETOPEC chemotherapy when GM-CSF support was routinely administered. Our relatively small sample size does not allow definitive conclusions regarding clinical benefit, but we showed no improvement in either rates of admission to hospital with fever or in chemotherapy DI. Further strategies of cytokine support and peripheral stem cell rescue are currently being studied in conjunction with continued escalation of the VETOPEC regimen.

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